PLAGUE

Introduction and History of Natural Infection

Plague is a zoonotic infection caused by *Yersinia pestis*, a Gram-negative bacillus. Naturally occurring infections in humans are transmitted from rodents by fleas and are characterized by the abrupt onset of high fever, painful local lymphadenopathy draining the exposure site, and bacteremia. Three forms of plague are recognized:

1. Bubonic plague – Characterized by the presence of buboes, the inflammatory swelling of one of more lymph nodes, usually in the groin;
2. Septicemic plague – Plague sepsis which can ensue from either untreated bubonic plague or *de novo* from a flea bite;
3. Pneumonic plague – Patients with bubonic plague can develop secondary pneumonic infection, which can then be spread from person-to-person without the need for transmission through a flea vector.

The etiologic agent of plague was first isolated in 1894 by Alexandre Yersin, who also made the connection between rats and plague, and independently by Shibasaburo Kitasato. The role of the flea was determined in 1897 by Masanori Ogata and Paul-Louis Simond, also independently of each other.

The oldest possible reference to bubonic plague may be contained within the biblical book of I Samuel. Plague has also been suggested as a causative agent of the Plague of Athens, which contributed to the defeat of Athens by Sparta in the Peloponnesian War (430 BC), although other bacterial and viral diseases have also been postulated.

Three major pandemics of plague have been noted in history. The first identifiable pandemic, the Justinian Plague, occurred between 541 and 544 CE, spreading from Ethiopia into Egypt and throughout the "known world" of the time (North Africa, Europe, central and western Asia, and Mediterranean Europe). Epidemics stemming from this pandemic continued into the 7th century CE, possibly contributing to the decline of the Byzantine Empire.

The second pandemic was the infamous "Black Death," which struck Asia and Europe in the 14th century. Traveling along the Silk Road from Asia through the 1330s, plague was noted at the Black Sea port of Caffa in 1346 and spread to Europe in 1347. By the end of the 14th century, it is estimated that the plague claimed over 40 million lives, or one-third of the population of Europe. Epidemics continued to occur, albeit infrequently, through the 1600s.

The third pandemic probably began in China in 1855. From there it spread to Hong Kong and disseminated, mostly by steamship, to Africa, Europe, the Middle East, India, the Philippines, North and South America, Hawaii, and Japan by 1900. Although effective public health and rat control measures kept the mortality rate of this pandemic

much lower than that of the previous two, stable enzootic foci became established on every continent except Australia.

History of Development as Weapon

The first attempt to use plague as a weapon occurred during the initial years of the Black Death. During the conflict between the Tartars and Genoese sailors at Caffa in 1346-7, the Tartars were struck with plague. The Tartar commander catapulted the corpses of his plague-infected soldiers at the Genoese. Plague broke out among the Genoese troops, more likely spread by local populations of infected rats than by the corpses, and the Genoese fled back to Italy.

During World War II, the Japanese army established a secret biological warfare unit in Manchuria, known as Unit 731. Plague was studied extensively, as it could create casualties out of proportion to the number of bacteria disseminated, could be used to make a very dangerous weapon, and its origins could be concealed to appear as a natural outbreak. One of the major breakthroughs of this group was the use of the human flea, *Pulex irritans*, as a delivery vehicle in bomb- or spray-based dissemination system. The Japanese apparently used plague as a weapon in China at least three times and possibly more during WWII.

The Soviet Union, as part of their wide-reaching biological weapons program, developed weaponized forms of *Y. pestis* in the 1970s and 1980s. These included a genetically engineered, dry, antibiotic resistant form of the bacterium. Several other countries, such as North Korea, the US, and Canada either have active research programs working with plague or have had such programs in the past.

Plague has never been used as a weapon against United States forces. Troops have been deployed in areas where plague is endemic. During WWII, a small outbreak occurred on the island of Hawaii, where plague has been endemic since 1899 (during the third pandemic). The outbreak was contained by means of rat control measures; in addition, it was official policy during WWII to vaccinate US troops with a killed plague vaccine. During the Vietnam War, only eight US servicemen were infected with plague, although Vietnam has been an endemic area for plague since 1898.

Etiology

Bacteriological Characteristics

There are 11 species of bacteria belonging to the genus *Yersinia* (family *Enterobactericeae*). Three of these, *Y. pestis*, *Y. pseudotuberculosis*, and *Y. enterolitica*, are pathogenic to humans. *Yersinia pestis* is a Gram-negative, nonmotile, non-spore-forming coccobacillus that is 0.5-0.8 μm wide and 1-3 μm long. It is a facultative anaerobe, and displays characteristic bipolar staining with Giemsa, Wright, and Wayson stains. *Y. pestis* has a cell wall and whole-cell lipid composition similar to that of other enteric bacteria and a "rough" lipopolysaccharide, containing only core components and lacking O-group side chains.

Bacterial genetics

Over the past decade, there have been significant advances in the study of genome structure, gene transfer systems and global regulation of virulence genes in *Yersinia pestis*. These studies have revealed a wealth of information about virulence mechanisms employed by *Y. pestis* to evade the host immune response.

Disease Ecology and Modes of Transmission

Life Cycle e - Vector

Plague is a zoonotic disease that primarily affects rodents. The oriental rat flea, *Xenopsylla cheopis*, is the classic vector for plague, though at least 31 species of flea are also proven vectors. In plague endemic areas, all fleas are considered potential vectors for the disease. In the United States, the most important vector of human plague is *Diamanus montanus*, a flea commonly found on California ground squirrels and rock squirrels.

Two days after ingestion of an infected blood meal, small clusters of *Yersinia pestis* can be observed in the flea gut. These clusters will eventually develop into cohesive masses composed of a fibrinoid-like material (most probably hemin) and mature *Y. pestis* bacilli. Three to nine days after the blood meal, these masses extend through the gut and esophagus, eventually blocking the proventriculus and preventing subsequent blood meals from reaching the gut. Normally, the proventriculus functions to prevent regurgitation of a blood meal. As the hungry flea repeatedly attempts to feed, uninfected blood from the mammalian host distends the blocked esophagus, mixes with bacilli, and is regurgitated into the mammalian host at the end of the feeding attempt. It has been estimated that 11,000 to 24,000 bacilli are regurgitated into the host during these events. While transmission of the disease cannot occur in fleas without gut and proventricular blockage, many 'blocked' fleas die of starvation and dehydration before host infection occurs.

Several factors affect the ability of infected fleas to transmit the disease to their mammalian hosts. At higher environmental temperatures, fleas are more likely to clear the infection and less likely to experience the gastrointestinal 'blockage' described above. This is possibly due to temperature regulation of hemin storage and the activities of certain essential proteases. *X. cheopis* quickly desiccates in hot and dry weather when away from the host, but stays viable at temperatures between 20^{o}C and 26^{o}C with humidity above 65%. Under these conditions, in fact, the fleas can survive for up to 6 months without a meal. The method of feeding (capillary vs. wound or "pool" feeding) also has implications for the efficiency of disease transmission; research in this area is ongoing.

Life Cycle - Mammalian Hosts

As mentioned, rodents are the primary enzootic reservoir for plague. Studies of enzootic infection are complicated by the fact that rodents tend to have a heterogeneous response to plague infection. Studies have demonstrated a direct correlation between the level of bacteremia in infected rodents and the percentage of infected fleas in particular geographic locations. A rodent bacteremia of 10^4 colony-forming units/ml has been correlated to the ingestion of 300 *Y. pestis* organisms per flea.

There are many mammals in the United States that can serve as reservoirs for plague infection. It is important to note that certain mammal-flea pairs are particularly at risk

because they contain a flea known to bite humans and a highly susceptible mammal. These include the rock squirrel, *Spermophilus variegatus* and the *Diamanus montanus* flea, both commonly found in California and the Southwestern states.

Transmission to Humans

It is important to note that humans are accidental hosts in the plague life cycle. Humans have no significant role in the long-term survival of the organism; the maintenance of *Y. pestis* in animal reservoirs is not dependent on human modes of disease transmission (ingestion, direct contact with infected persons). The maintenance of *Yersinia pestis* in the natural environment is entirely dependent upon cyclic transmission of the organism from fleas to mammals. Plague epidemics are most likely to occur in areas that have inadequate sanitary conditions and large populations of rats.

In nature, plague is either enzootic or epizootic. Enzootic infection is characteristic of a stable rodent-flea infectious cycle where the host is relatively resistant to the disease. In the enzootic state, the morality rate of infected rodents is usually low. Fortunately for humans, when the disease is in an enzootic state, the fleas have no reason to acquire less desirable hosts, such as humans.

In an epizootic, however, bacteria are introduced into susceptible mammalian hosts, like prairie dogs and humans. In these cases, mortality rates in the susceptible hosts tend to be quite high. Humans are most likely to acquire plague by the following mechanisms:

Source of Infection	Mechanism of Infection
Fleas with other mammalian hosts	Flea bites, inoculation of flea feces during bites.
Fleas whose hosts are usually human	Flea bites
Infected animals	Consuming infected tissue, aerosols, draining infected abscesses, handling infectious hides or pelts.
Other humans	Direct contact with infected body fluids, aerosols.

Human-to-human transmission of plague occurs from persons with pulmonary *Y. pestis* infections. There is still much to be learned about the epidemiology of pulmonary pneumonic plague, but it appears that close contact, moderate humidity, and cool climate are required for successful transmission of the infection. In tropical climates, outbreaks of pneumonic plague are rare even during bubonic plague epidemics.

Epidemiology

A total of 18,739 cases of plague in humans in 20 countries (in Africa, Asia, and the Americas) were reported to the World Health Organization from 1980-1994. The average number of global cases per year was 1,087. The countries with the highest number of reported cases during this period include Madagascar, with 1,390 cases and 302 deaths; Tanzania, with 4,964 cases and 419 deaths; and Zaire, with 2,242 cases and 513 deaths. High mortality rates have been reported in other several other countries in Latin America and Sub-Saharan Africa. It is important to note that the incidence of plague is underreported in those countries where laboratory capabilities and surveillance methods are limited.

In the United States, the majority of human plague cases occur in the summer months because the risk of exposure to infected fleas is highest during this time. Between 1970 and 1995, 341 cases of plague in the US were reported to the Centers for Disease Control, with an average of 13 cases per year. Eighty percent of these cases occurred in the southwestern states of Arizona (14%), Colorado (10%) and New Mexico (56%). An additional 9 percent of cases were reported from California. In these states, it was observed that the majority of cases were acquired on or around the patient's home. Less often, the infection was acquired while patients were engaged in outdoor work or recreational activities, with the latter cause most prevalent in California.

Cellular and Molecular Pathogenesis

Much is currently known about the chromosomal and plasmid-associated factors that contribute to *Y. pestis* virulence and host survival. An important focus in the study *Yersinia* spp. pathogenesis has been to investigate why *Yersinia pestis* is more invasive to the human host than *Y. enterocolitica* and *Y. pseudotuberculosis.* Fortunately, *Y. pestis* has 90% DNA sequence homology with the much less invasive *Y. pseudotuberculosis*, making it possible to isolate and study genes expressed only by *Y. pestis*.

As with all *Yersinia* species, *Y. pestis* contains several 70- to 75- kilobase-pair (kbp) plasmids that carry the virulence genes. Among the factors associated with this plasmid are the Yop proteins. Originally, the term Yop stood for *Yersinia* Outer membrane Proteins. It has since been determined that these proteins, which contribute to host survival by interfering with signal transduction and affecting the host cell cytoskeleton, are secreted proteins that will only associate with the membrane under certain conditions.

Y. pestis is unique in that it carries two additional plasmids, at 110 and 9.5 kbp, which are not found in the other *Yersinia* species. These plasmids code for an antiphagocytic capsule and a plasminogen activating factor, respectively. It is suspected that these two extra plasmids, and the virulence factors they encode, are responsible for the increased invasiveness of *Y. pestis* when compared with other *Yersinia* species.

The major virulence factors involved in *Yersinia pestis* pathogenesis are summarized in the following table.

Virulence Factor	Putative Function
Fra1 (antiphagocytic fraction 1 capsule)	Unique to *Y. pestis*, this factor forms the protein capsule that prevents phagocytosis. The gene for Fra1 is encoded on the 110 kbp plasmid.
PsaA (pH 6 antigen)	A pilus adhesin which is produced maximally at pH=6. May be produced in response to ingestion into the phagosome.
Yop H	Tyrosine phosphatase that interferes with phagocyte signal transduction. Prevents phagocyte migration toward bacteria.
Yop E	Cytotoxin that destroys host phagocyte actin monofilaments and promotes cell death.
Yop M	Competes with platelets for α-thrombin, preventing the release of inflammatory mediators that would normally stimulate phagocyte activity.
LcrV (V antigen)	Function unknown, but appears to be essential in the expression of Yops.
Pla (plasminogen activating factor)	Protease that activates plasminogen and evades complement killing by degrading C3b and C5a.

Environmental factors in the human host, such as contact with eukaryotic cells, elevated temperature and the location of bacteria within cells (or in necrotic foci at low pH) may activate the synthesis and expression of virulence factors. It is important to note that,

since *Y. pestis* bacilli are injected into the host by the insect vector, virulence factors for tissue adhesion and invasion are not present.

In addition, *Y. pestis* bacilli are resistant to serum-dependent killing by the membrane-attack complex (MAC) produced during the complement cascade. Unlike the other *Yersinia* species, *Y. pestis* is serum resistant at all temperatures. This is likely due to the requirement of the bacilli to evade complement-mediated killing in both the insect vector and the mammalian host. Although not much is known about the exact mechanism of complement evasion, it is likely that the extracellular Pla protease prevents MAC formation.

Organ and System Pathogenesis

In the case of insect bite transmission, bacteria injected into the blood travel to the nearest lymph node, where bacteria are ingested by tissue macrophages. It has recently been suggested that, at ambient temperature, the bacilli are susceptible to phagocytosis and killing by neutrophils. However, the *Y. pestis* bacillus can multiply and survive in normal, unactivated macrophages once its virulence genes are activated, resulting in local proliferation of the bacteria in the lymph nodes. The inflammatory response to lymphatic proliferation creates the characteristic suppurative lymphadenitis, or bubo, associated with bubonic plague. Buboes most commonly appear in the region of the femoral lymph nodes. The inguinal, axillary, and cervical areas are the next most common. As mentioned, location of the bubo is a function of the location at which the infected insect inoculates *Yersinia* bacilli. Dissemination of the bacilli from the site of injection to the regional lymph nodes is mediated by the action of plasminogen activator and Yop M.

In some cases, bacteria in the lymph nodes will leak into the peripheral circulation, causing secondary septicemic plague. This form of the disease is considered secondary because it developed as a complication of the hematogenous dissemination of bubonic plague. Septicemic plague can also appear primarily from infected fleabites. Lysis of bacteria in the bloodstream releases lipopolysaccharide (LPS), leading to classic Gram-negative sepsis and septic shock. The presence of LPS in the blood will often lead to intravascular disseminated coagulation, resulting in necrotic lesions in the peripheral blood vessels. These lesions give the skin the blackish appearance, from which the name “black death” derives.

Viable bacilli can also migrate to the lungs and invade alveolar macrophages, resulting in a secondary pneumonic plague (stemming from the primary bubonic infection). Pneumonic plague patients are highly contagious and can transmit the disease by aerosol. The case-fatality rate for untreated pneumonic plague is close to 100% and patients usually die within days.

Direct inhalation of infective aerosols results in a primary pneumonic plague, which progresses much more rapidly than the other forms of the disease. Current theories suggest that the aerosolized bacteria released from a pneumonic case are already expressing the virulence factors needed for effective colonization of the human host, reducing the time of disease progression in these cases.

Clinical Manifestations

Basic statistics on the presenting cases of the three forms of plague are given in the following table.

Clinical Form	General Description	Percent presenting cases in naturally occurring infection
Primary cases		
Bubonic	Occur via infected flea or insect bites resulting in inflammatory response at the infected regional lymph node.	85-90%
Primary septicemic	Develops directly from infected flea/insect bite, results in blood coagulation and characteristic purpurea/ peripheral necrotic lesions.	10-15%
Primary pneumonic	Caused by human-to-human transmission via aerosol resulting in the infection of alveolar macrophages.	1%
Secondary Cases		
Secondary septicemic	Result from hematogenous dissemination of primary bubonic plague	23% of those presenting with bubonic plague
Secondary pneumonic		9% of those presenting with bubonic plague

It is critical to note that these statistics reflect *naturally occurring infection*, where infected fleabites are most likely responsible for transmission of the disease. If *Yersinia pestis* were used as a biological weapon, it would likely be dispersed via aerosol. Clinical manifestations would indicate epidemic pneumonia, with evidence of blood in the sputum. In the less likely event that infected fleas were deliberately released as carriers, patients would present with symptoms of bubonic or septicemic plague (discussed below).

Clinical Manifestations of Bubonic Plague

I. Subjective Symptoms- all of the following are considered presenting symptoms.

Symptom	Percent of presenting cases	Time of onset
sudden fever/chills	40%	After 1-8 day incubation period
headache	20-85%	
nausea/vomiting	25-49%	A few hours after appearance of fever, chills and/or headache.
prostration/severe malaise	75%	
altered mentation	26-38%	

cough	25%	
chest pain	13%	
abdominal pain	18%	

II. Objective Symptoms

Organ/System	Description	Period and Duration
Skin	Appearance of characteristic and intensely painful plague bubo (femoral site most common, followed by inguinal, axillary and cervical).	Manifestation: buboes appear after a 1-8 day incubation period and 6-8 hours after the onset of the symptoms described above.
Genitourinary	bladder distention oliguria and anuria	Manifestation: around the time that bubo appears.
Circulatory cardiac blood	 Tachycardia Hypotension Leukocytosis	Manifestation: around the time that bubo appears.
Respiratory	5 to 15% of patients will develop secondary pneumonic plague	See objective symptoms of pneumonic plague.
Immune	pronounced septicemia	See objective symptoms of septicemic plague.

Clinical Manifestations of Septicemic Plague

I. Subjective Symptoms- all of the following are considered presenting symptoms and are generally the same as those for any other Gram-negative sepsis:

Symptom	Form of septicemic plague	Time of onset
fever/chills	usually primary only	Primary: after 1-8 day incubation period Secondary: 2-6 days after appearance of plague bubo
nausea/vomiting	primary and secondary	
diarrhea	primary and secondary	

II. Objective Symptoms: The only unique, objective symptoms of primary or secondary septicemic plague are purpuric lesions, disseminated intravascular coagulation and acral cyanosis and necrosis. These are seen at least 4-6 hours after the onset of symptoms described above.

Clinical Manifestations of Pneumonic Plague

As mentioned, pneumonic plague occurs either primarily from aerosol inhalation or secondarily from hematogenous dissemination from bubonic plague. The subjective symptoms are the same as for bubonic plague. The objective clinical presentation of pneumonic plague is limited to a productive cough with blood-tinged sputum occurring 24 hours after onset of symptoms.

Diagnosis

If the patient presents in a non-endemic area without a suspicion of biological attack, to a physician who is not familiar with the disease, making a positive diagnosis for plague will be extremely difficult.

Differential Diagnosis of Bubonic Plague
For a patient presenting with a bubo, the differential diagnosis should include the following:
(1) Tularemia: inoculation site should be more evident and the patient should not be septicemic
(2) Chanchroid: inoculation site should be more evident, no sepsis, less local pain, and a recent history of sexual contact and genital lesions,
(3) Lymphogranuloma venereum: a recent history of sexual contact and genital lesions.
(4) Streptococcal adenitis: although difficult to distinguish initially, patient should not be septic and the bubo-associated lymph node should be less tender than in plague.
(5) Scrub typhus: less local pain and no sepsis.

Tuberculosis should also be included in the differential diagnosis.

Differential Diagnosis of Septicemic Plague
The differential diagnosis of septicemic plague should include:
(1) Meningococcemia
(2) Other Gram-negative sepses
(3) Rickettsioses

Differential Diagnosis of Pneumonic Plague
A patient who presents with systemic toxicity and a productive cough with bloody sputum indicates a broad differential diagnosis. However, the confirmation of Gram-negative rods in the sputum should quickly suggest plague infection, since *Y. pestis* may be the only Gram-negative bacillus that can cause extensive pneumonia with bloody sputum in an otherwise immunocompetent host.

A large influx of patients with the symptoms noted above would be suggestive of a deliberate biological attack. In such a scenario, inhalational anthrax would be included in the differential. The hemoptysis characteristic of pneumonic plague would be a useful clinical indicator.

Laboratory Diagnosis

Several laboratory tests are available to assist with diagnosis. In a patient with compatible clinical manifestations, the presence of Gram negative, bipolar staining coccobacilli from clinical tissues (i.e., bubo, blood, or tracheal/lung aspirate for bubonic, septicemic, or pneumonic forms respectively) satisfies the criteria for a suspected case of plague. Note that it may take up to 72 hours to obtain final culture and sensitivity results.

Other rapid diagnostic tests available include antigen detection and immunostaining that target the Fraction 1 antigen unique to *Y. pestis*. An ELISA test is also available, as is confirmatory testing using PCR techniques. The passive hemagglutination assay used for antibody detection is less useful, as antibody development does not occur until several days to weeks after onset of symptoms.

Disease Prevention

Transmission control

Public health measures to control the transmission of plague must include proper sanitation, insecticide use, rodent population reduction (with chemicals like calciferol) and public health education. In vector control efforts, fleas should always be targeted before rodents, because the killing of rodents could release massive numbers of infected fleas. Proper garbage disposal and the elimination of crowded living conditions with substandard housing must be accomplished to decrease the contact frequency between rodents and humans. Hikers in the Western US should avoid contact with wild rodents and keep food sealed in airtight containers. Hunters and trappers should wear gloves when handling wildlife.

Post-exposure prophylaxis

Any individuals who have been exposed to aerosols should receive post-exposure prophylaxis for 7 days. Current recommendations from the Working Group on Civilian Biodefense are for doxycycline 100 mg twice daily for adults, including pregnant women, and children >=45 kg. Children under 45 kg. should receive 2.2 mg/kg orally twice daily. For further details, consult the abstract of the Working Group's paper[1] available from the CDC website at: http://www.bt.cdc.gov/agent/plague/index.asp

Immunization

No plague vaccine is currently available for use in the United States, although a killed vaccine was previously licensed. Animal and preliminary human studies have indicated that a killed plague vaccine is not effective for preventing pneumonic plague. A recombinant vaccine candidate for the prevention of pneumonic plague after inhalational challenge is currently being evaluated.

Treatment and Therapy

(1) Isolation

All patients with confirmed plague infection must be isolated for the first 48 hours following initiation of treatment. Hospital staff must exercise special caution when handling blood, sputum, or bubo discharge. If a patient has a confirmed case of pneumonic plague, then strictly enforced airborne infection isolation, including droplet precautions, must be followed. This includes the use of gowns, gloves, masks/face shields and eye protection. These patients must remain isolated until they have completed at least 4 days of antibiotic administration. Patients may be removed from isolation if they have no draining lesions or pneumonia after 48 hours.

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[1] Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: Medical and public health management. JAMA, May 3, 2000; vol. 283, no. 17: 2281-2290.

(2) Antibiotic Treatment

Antibiotic treatment is essential for treating plague. Without treatment, mortality is 60% for bubonic plague and 100% for septicemic plague. Since time-to-death is relatively short, the earlier the treatment is initiated, the more favorable the outcome. Patients are not likely to survive primary pneumonic plague if a course of antibiotics is not initiated within the first 18 hours of symptom onset. Plague buboes will subside in 10-14 days if treated with antibiotics.

Since 1948, streptomycin has been the preferred choice for the treatment of bubonic, septicemic, and pneumonic plague, although clinical isolates with plasmid-mediated streptomycin resistance have been reported [Guiyoule A et al. EID 2001; 7(1):43-8]. Streptomycin should be administered intramuscularly. Although gentamycin has been used less frequently, it can be used as an alternative treatment to streptomycin. Alternate choices in a contained casualty setting include intravenous doxycycline, ciprofloxacin, or chloramphenicol. Treatment should always continue for at least 10 days or for 3-4 days after clinical recovery. Specific recommendations regarding dosages for adults, children and pregnant women are included in the consensus statement from the Working Group on Civilian Biodefense[1]. Note that oral therapy, preferably with doxycycline, may be the only option feasible in the event of a mass casualty scenario. Clinicians should consult with public health authorities for any updates to these recommendations.

Safety Procedures

Handling

Wild-type *Yersinia pestis* organisms can be handled safely in laboratories using standard microbiological methods. Processing of potentially infectious clinical specimens should use Biosafety Level (BSL) 2 containment procedures. Work that involves a high potential for the generation of aerosols or with large amounts of the bacteria should be done in BSL-3 conditions. Bacteria with suspected or confirmed antibiotic resistance should also be handled under BSL-3 conditions.

Reporting

All cases of plague must be reported to local public health authorities in all 50 states. The local authorities must notify the appropriate federal government officials and the World Health Organization, as international travelers suspected of plague infection may be quarantined for up to six days under international law. The extremely high level of contagion and high mortality and case-fatality rates associated with pneumonic and septicemic plague (the most likely outcomes in a biological attack) underscore the importance of swift and accurate reporting.